Mathematical Modeling of Cancer Cells and Chemotherapy Protocol Dealing Optimization Using Fuzzy Differential Equations And Lypunov Stability Criterion

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Abstract

Mathematical models can simulate the growth and proliferation of cells in the interaction with healthy cells, the immune system and measure the toxicity of drug and its effects on healthy tissue pay. One of the main goals of modeling the structure and growth of cancer cells is to find a control model suitable for administration among patients. In this study, a new mathematical model is designed to describe the changes in different phases of the cycle T cell proliferation, the population of immune cells, the proposed concentration of drug toxicity and treatment using differential equation and fuzzy Lyapunov stability, an optimal treatment protocol. One feature to consider is the rate of clearance of the drug in the body.

Keywords: The optimal treatment protocol, Mathematical modeling of cancer, fuzzy differential equations, Lyapunov stability criteria

1- Introduction

Cancer is one of the most important factors of human morbidity and mortality; throughout the world there has always been the department of engineering science professionals' attention and basic science courses and extensive research and modeling in ways its treatment has taken place. Among the methods of cancer treatment, chemotherapy has been considered useful as a significant side effect, with serious damages to the healthy tissues of the patient. By optimizing the timing of injection, drug harms of this treatment can be reduced to a low level. For this purpose mathematical model system is necessary. Mathematical models can simulate the growth and proliferation of cancer cells in contrast to healthy cells of the bodies' immune system and chemical agents used in the treatment of cancer and ensuring and measuring the toxicity of drug and its effects on healthy tissue pay. Mathematical models for cancer, depending on the model and level of detail provided, are intended to include a large variety of different types of differential equations. Obviously, a reliable protocol designed to be a more accurate Mathematical model was used to simulate system behavior [22, 23]. Mechanism of action of chemical agents used to treat cancer is that cells in a particular phase of proliferation (including phases G_1, s, G_2, u) has held and to continue

advancing in the cycle stops, the immune cells to attack cancer cells and destroy them normally. For example, drugs (Ara-C) cytosine, Arabino side, 5- Flourouraeil, and prednisone are among them. In phases G_1, s and drugs vincristire, pacliture and Bleomycin act in m phases[1], [2]. Many mathematical models are offered, all of the cancer cells in a tumor population considered[3], [6]. But on closer look, since most drugs on cancer cells in a specific phase of the cycle affect cell proliferation, the middle population density of cancer cells in different phases of the cycle will provide treatment closer to the real system. Including recent research on the modeling of cells in different phases of the cell cycle, works of webb[7], kheifetz[8], Brikhead [9] and Swan [10] can be noted. Chemotherapy drugs' act in particular in their review article mentioned has been mentioned. Pannetta and Kirschre[11], the effects of the immune system as an adjunct in the chemotherapy are considered. Villasana[12], chemotherapy drugs act in a particular phase, as well as the effects of immune cells in the model, but the model did not consider the rest of cells. Kuzusko[13], based his idea on experimental data and mathematical models. To study the interaction between cancer cells and a drug operation, a particular phase has to be offered. A complete study in the field of mathematical modeling and control of cell proliferation cycle was carried out by Kimmel and Swierniak [4]. The conventional method for designing an optimal treatment protocol was introduced using the classical optimal control[14] , [15].

In[3], a complete summary of recent efforts in the field of modeling control the growth of cancer cells is provided. In this paper, in the second part, a new mathematical model to describe the changes in different phases of the cell cycle T cell proliferation, the concentration and cytotoxicity of immune cells have been suggested. The third section is a short description on the balance system. In part four, with the introduction of a candidate Lyapunov function, asymptotic stability control law to ensure the overall results and in part five, with the control, protocol design for a hypothetical patient would return results.

2- Mathematical Modeling

The model in this study, changes in four cell populations, the concentration of the chemical drug used and provided. This model is similar to models [12] , [16] which will provide the correct words to them, but they are fundamentally different. Frist, the models [12] , [16] change healthy cells in the population not considered. The effect of drugs on the tissue due to the side effects of chemical drugs is essential. The changes in toxic chemical agents, as a parameter to see the effect of the dragon healthy tissue of the patient, single phase differential equation models will be added. The second difference is easy access if medication based on Lyapunov stability theorem using Fuzzy differential equation, dynamic effects rather than final in front of the Mass- action has been taken into consideration. The model presented in this study matched the growth

of healthy cells and cancer cells and the growth is assumed to be final. Population changes in cancer cells in different phases of cell cycle individually and through the cells of the middle phase is considered. Competition of immune cells and cancer cells in a model of prey- predator is assumed. Patients' blood plasma is mixed and their effects on tissue caused cancer. The effect of chemical drugs – induced toxicity on immune cells is observed. Accordingly, the model for Fuzzy differential equations a bunch (DDE-delayed) the following shall be provided in accordance with the:

$$\dot{x} = \alpha_3 z - \alpha_1 x - \delta_1 x - K_1 I_x \quad (1)$$

$$\dot{y} = \alpha_1 x(t-\tau) - \alpha_2 y - \delta_2 y - K_2 Iy - K_4 uy \quad (2)$$

$$\dot{z} = z\alpha_2 y - \alpha_3 z - \delta_3 z - K_3 I_2 \quad (3)$$

$$\dot{I} = K + \frac{\rho I(x+y+z)^h}{\alpha + (x+y+z)^h} - \delta_4 I - (c_1 x + c_2 y - c_3 z)I - K_6 uI \quad (4)$$

$$\dot{u} = V - \gamma\eta \qquad ,\dot{s} = u - \eta s \quad (5)$$

In the above equation [x(t)] of cancer cells in the intermediate phase, [y(t)] of cancer cells in the mitosis phase, [z(t)] population as cancer cells in the stationary phase, [I(t)] the population of immune cells, [u(t)]the drug concentration and [s(t)] shows the effects of the drug. Basically, the Fuzzy differential equation with positive initial conditions are $y(o)=y_0$ $z(o)= z_0$ $I(o)= I_0$, $x(t)=\emptyset_1(t)(t \in [-\tau, 0])$, $u(0)=u_0$, $s(o)= s_0$ The equation is shown as $\dot{x}$, describing the changes population cancer cells present in the middle phase (G_1 , s , G_2), respectirely. In the equation $\alpha_3 z$ arrival rate of cells in stationary phase, middle phase shows. In this case, it is assumed that cells in the stationary phase accidentally have left this phase, the either start its activities in the cell cycle or are released into the bloods' stream (in other words, with a cell death). Phrases $\alpha_1 x$, $\delta_1 x$, are in the rate of cancer cells from the middle phase to phase of mitosis cancer cells by the immine cells as a competitive show words $k_1 I_x$, the death rate of cancer cells by the immune cells as a competitive show. The equation $\dot{y}$ describes changes of cancer cells in the mitotic phase. In this equation $\alpha_1 x(t-\tau)$ shows arrival rates of cancer cells from the middle phase to mitosis phase. Now, at the beginning of mitosis phase of the cell it assumes τ days before the beginning of the middle phase. The time spent getting ready for introduction into the cell nucleus DNE is amplified [12]. $\alpha_1 y$ rate of cancer enters mitosis phase to the stationary phase shown. $\delta_1 y$ and $k_2 Iy$ the same equation ago and $k_4 uy$ the death rate of cancer cells by chemical drugs shows $\dot{z}$ population changes in cancer cells in stationery phase (G_0) is described. In this equation, $z\alpha_2 y$ the rate of cancer cells enters mitosis phase to the stationary phase shown.

Factor 2, represents a doubling of the number of cells in mitosis process. $\alpha_3 z$, $\delta_3 z$, $k_3 I_z$ are similar to previous models. $\dot{I}$ describes the population dynamics of immune cells. Immune cells are a constant source of growth rate constant (k). Immune cells stimulate the growth of cancer cells with an expression "Michael is menten", "$\frac{eI\,(x+y+z)^h}{\alpha+(x+y+z)^h}$" shown. $\delta_4 I$ immune cells show normal death rate. It is assumed that some immune cells, censer cells become inactive in the face of this event in the $(c_1 x + c_2 y + c_3 z)\, I$ is modeled. $k_6 uI$ is immune to death by chemical drugs. The rate of drug concentration in the body is modeled $\dot{u}$ equation. It was supposed to end the drug in the body decreases. And half – life of the drug and concentration effects in the body as $\dot{u} = -yu$, indicates the dose received.

Table.1. Definitions of constants in the equation and the values obtained for each system state

System constants	Definition	Parameter (for e given patient)	Obtaining source
α_1	rate through which cell flows into the mitosis phase	1/ day	[12], [16], [17]
α_2	rate through which cell flow into the resting phase	0.6/ day	[16], [17]
α_3	rate through which cells leave from the resting phase to enter the cycle to reproduce	0.9/ day	[16], [17]
c_1	losses due to the encounters with immune cells	0.2×10^{-6}/ cell day	[12], [17]
c_2		0.8×10^{-6}/ cell day	[12], [17]
c_3		0.108×10^{-6}/ cell day	[12], [17]
δ_1	proportions of natural death of x, y, and I	0.11/ day	[12], [17]
δ_2		0.28/ day	[12], [17]
δ_4		0.3/ day	[12], [17]
δ_3	rate through which cells leave from the resting state to enter the blood	10^{-5}/ day	[16], [17]
p	proportions of the growth of lymphocytes due to stimulus by cancer cells	0.2/ day	[12], [17]
a	speed at which the lymphocytes reach saturation level without stimulation	$0.5 \times (10^5 \text{ cell})^1$	[12], [17]
k	Growth rate of the lymphocytes in the absence of cancer cells	0.15×10^6 cell /day	[12], [17]
k_1	rate a which lymphocytes destroy cells in different phase	10^{-8}/ cell day	[12], [17]
k_2		0.4×10^{-8}/ cell day	[12], [17]
k_3		0.1×10^{-8}/ cell day	[12], [17]
k_4	Proportion of drugs which eliminates cancer cells and lymphocytes	0.25/ mg- day	[12], [17]
k_6		0.03/ mg- day	[12], [17]
τ	Resident time of cells in the inter phases (Daley)	0.5/ day	[12],[16], [17]
η	Rate of drug toxicity decay	0.5/ day	[6]
γ	Proportion of decay of the drugs	0.03/ day	[12]

The relationship between toxicity and concentration in the body is modeled by the equation $\dot{S} = u - ns$. Rate of change of the rate of drug toxicity and drug concentration in the body are directly likened. In Table 1 system parameters and their values for a hypothetical patient have been described.

3- Balance of System

In a dynamic system as a whole $\dot{X} = F(x)$, the non – linear Function F, the balance of the system is not unique, and sometimes it is difficult to identify all of them. As always, during the balance of system analysis are considered, to study these points and the point that is closer to conditions selected.Of the balance of the system, $(o, o, o, \frac{1}{\delta_4})$ point indicating the zero point to the number of cancer cells and an acceptable is level of cell safety (the ultimate goal of cancer treatment). The point at the zero level for the concentration and toxic of the drug, as a healthy balance for your analysis and evaluation of the rest of the balance (the balance of death) are ignored. After determining the balance of the system, the first step is analysis of stability. To [18] a complete analysis of the stability of the balance of health, the results will be presented in a few cases. The delay has a significant effect on the stability of the system that can be unstable system sustainable mode or vice versa.

4- Stable Equilibrium Health

To design the optimal chemotherapy protocol based on lyapunor direct method, the function as the candidate Lyapunov was assumed after using Fuzzy differential equation, control law in a way that the candidate is supposed to be a lyapunor function. Lyapunov function, if the sphere of radius $B_{R,}r(x)$ is a given triangle and has Global stability, suppose a scalar function "r" the first order derivative system state variables are continuous, so:

In that case $\nu(x) \longrightarrow \infty$ that the equilibrium point at the origin is a stable equilibrium point totally asymptomatically [21]. Case: Balance point health, $E_0 = \left(0,0,0,\frac{k}{\delta_4},0,0\right)$, Asymptotic global stability is if:

Continuous partial derivatives on a direct path curve, the curve is determined by half ($\nu(x) \leq o$), in this case, the $\nu(x)$ a Lyapunov function will be for the system. This Function has been extended to system (as a whole $\dot{X}(t) = f(x_d,u)$) with time delay Lyapunov function –among Razamykhyan and Lyapunov – krashrf sky[19], [20]. Global stability, suppose a scalar function "r" the first order derivative system state variables are continuous, so:

In that case $\nu(x) \longrightarrow \infty$ that the equilibrium point at the origin is a stable equilibrium point total asymptomatically [22]. Case: Balance point health, $E_0 = \left(0,0,0,\frac{k}{\delta_4},0,0\right)$, Asymptotic global stability

As if:

$$u > \frac{\alpha_2 y}{k_4 y + \beta k_4 I\left(I - \frac{k}{\delta_4}\right)} \qquad (6\text{-a})$$

$$\beta = \min\left\{\frac{k_i}{c_i \frac{k}{\delta_4} + \frac{\sigma}{\alpha} I_m}\right\} \qquad (6\text{-b})$$

Proof: Lyapunor candidate function is defined as follows:

$$\begin{aligned}\nu = a\,[x + y + z &+ \alpha_1 \int_{\tau}^{0} x(t \\ &+ \xi)d\xi\,]\,\frac{d}{z}\left(I - \frac{k}{\delta_4}\right) \\ &+ eu + fs\end{aligned} \tag{7}$$

On the curve of the path system, a derivative v(x) will be as follows:

$$\begin{aligned}\nu(\omega) = a\,\Big[\overset{\circ}{x} + \overset{\circ}{y} + \overset{\circ}{z} &+ \alpha_1\{x(t) \\ &- x(t-\tau)\}\Big] \\ &+ d\left(I - \frac{k}{\delta_4}\right)\overset{\circ}{I} + \overset{\circ}{eu} \\ &+ f_s\end{aligned} \tag{8}$$

So we came to the conclusion:

$$\begin{aligned}\nu(\omega) = a\,[&\alpha_3 z + \alpha_1 x - \delta_1 x - k_1 I_x \\ &+ \alpha_1 x\,(x-\tau) - \alpha_2 y \\ &- \delta_2 y - k_2 I y - k_4 u y \\ &+ 2\alpha_2 y - \alpha_3 z - \delta_3 z \\ &- k_3 z I \\ &+ \alpha_1\{x(t) \\ &- x(x-\tau)\}] \\ &+ d\left(I - \frac{k}{\delta_4}\right)k \\ &+ PI\frac{(x+y+z)}{a+(x+y+z)} \\ &- \delta_4 I \\ &- (c_1 x + c_2 y + c_3 z)I \\ &- k_6 u I) + e(-yu) \\ &+ f(u - ns)\end{aligned} \tag{9}$$

After simplification, we have:

$$\begin{aligned}&\dot{\nu} \\ &= -a(\delta_1 x + \delta_2 y + \delta_3 z) \\ &- d\delta_4\left(I - \frac{k}{\delta_4}\right)^2 \\ &- d(c_1 x + c_2 y + c_3 z)I^2 \\ &+ \left(-a\alpha k_1 + dc_1\alpha\frac{k}{\delta_4}\right. \\ &\left.+ dpI_m\right)\frac{I_x}{\alpha + (x+y+z)} \\ &+ \left(-ak_1 + dc_1\alpha\frac{k}{\delta_4}\right. \\ &\left.+ dpI_m\right)\frac{I_x(x+y+z)}{\alpha + (x+y+z)} \\ &+ \left(-a\alpha k_2 + dc_2\alpha\frac{k}{\delta_4}\right. \\ &\left.+ dpI_m\right)\frac{I_y}{\alpha + (x+y+z)} \\ &+ \left(-ak_2 + dc_2\frac{k}{\delta_4}\right)\frac{I_y(x+y+z)}{\alpha + (x+y+z)} \\ &+ \left(-a\alpha k_3 + dc_3\alpha\frac{k}{\delta_4}\right. \\ &\left.+ dpI_m\right)\frac{I_z}{\alpha + (x+y+z)} \\ &+ \left(-ak_3 + dc_3\frac{k}{\delta_4}\right)\frac{I_z}{\alpha + (x+y+z)} \\ &+ \left(-ak_3 + dc_3\frac{k}{\delta_4}\right)\frac{I_z(x+y+z)}{\alpha + (x+y+z)} \\ &- d\frac{k}{\delta_4}p\frac{I}{\alpha + (x+y+z)} - ak_4 u I^2 \\ &+ dc_6\frac{k}{\delta_4}uI + u(r - ey) - f\,ns \\ &-ak_4 uy + a\alpha_3 y - dk_6 uI^2 \\ &\qquad + dk_6\frac{k}{\delta_4}uI < 0 \Rightarrow a \\ &\qquad < \frac{k_6 uI^2 - k_6\frac{k}{\delta_4}uI}{\alpha_3 y - k_4 uy}\,d\end{aligned} \tag{10}$$

However $\dot{\nu}$ because is negative, it must be negative sentences. Considering the fact that the number of cells and the concentration of

drug toxicity values should be no negative values:

$$d < \left[\left\{\frac{k_i}{k_i\frac{k}{\delta_4}+\frac{e}{a}Im}\right\}\right]a \qquad (11)$$

$$i = 1,2,3,\ldots$$

$$-ak_4uy + a\alpha_3 y - dk_6uI^2 + dk_6\frac{k}{\delta_4}uI < 0 \Rightarrow a < \frac{k_6uI^2 - k_6\frac{k}{\delta_4}uI}{\alpha_3 y - k_4 uy}d \qquad (12)$$

And finaly:

$$f < er \qquad (13)$$

The bare conditions: v(x) a Lyapunor function for the system. If the values e, f compared with a, b they would be too small. If we assume that the smallest amount of e, f as compared a, b, by placing one of the two relationships (11), (12), the other control law is obtained:

$$u > \frac{\alpha_2 y}{k_4 y + \beta k_6\left(I - \frac{k}{\delta_4}\right)} \qquad (14)$$

$$\beta = \min\left\{\frac{k_i}{c_i\frac{k}{\delta_4}+\frac{e}{\alpha}Im}\right\} \qquad (15)$$

5- Of the drug based on Fuzzy equations, and Lyapunor stability criteria

Parameters were given to the patient so that the equilibrium point is unstable health. The continuous partial derivatives on a direct parameter in table (1) have been given. The initial condition of the system behavior is obtained in the absence of chemotherapy.

$$x(t) = 3\times10^{+6}, y(t) = 3\times10^{+6}, z(t) = 4\times10^{+6}, I(t) = 2\times10^{+6}$$

Due to the unstable equilibrium of health systems around, it points to the death of Gil as one of balance. (Figures 1, 2) In figure 3 the way of the drug based obtained with the concentration and toxicity criteria Lyapunor and in the figure (4) changes in the population of cancer cells and immune cells of the protocol can be obtained. Forms (3), (4) 7 sessions of chemotherapy after about 50 days, the number of cancer cells has declined.

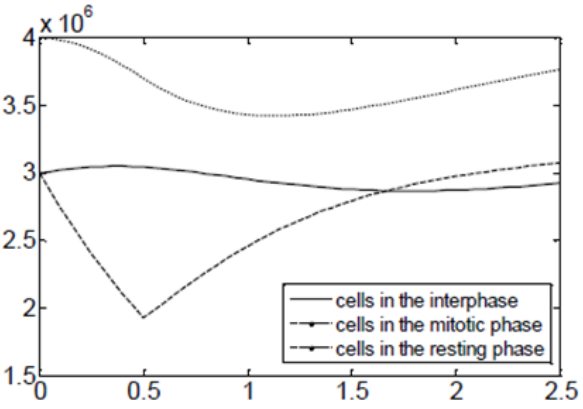

Fig.1. Change in the absence of cancer cells in different phases of the drug

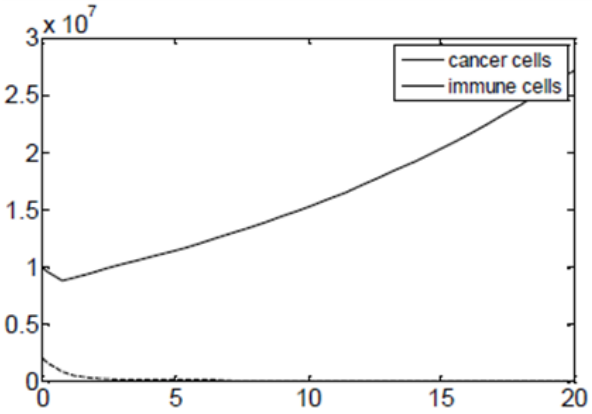

Fig.2. Change in the total population of cancer cells and immune cells in the absence of drug

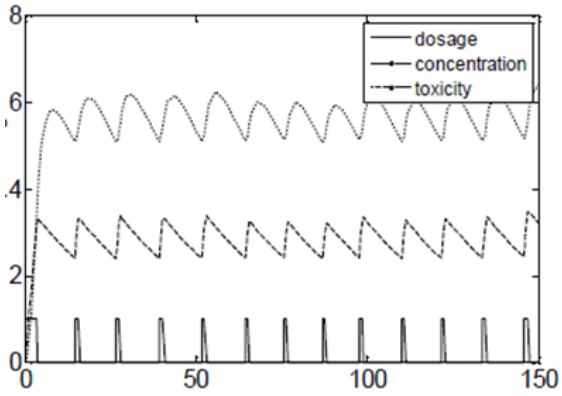

Fig.3. model drag dosage Lyapunov criteria in accordance with the concentration and toxicity

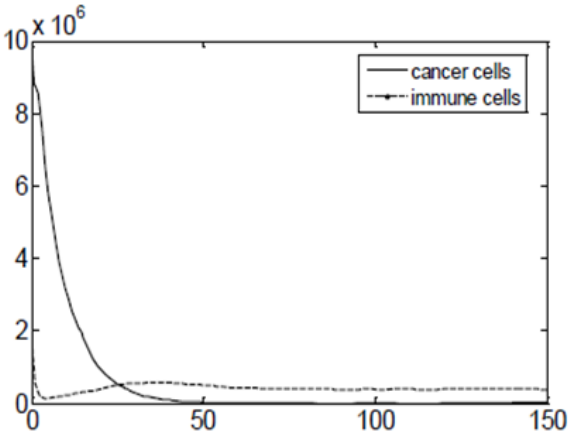

Fig.4. Change in the total population of cancer cells and immune cells consistent pattern of figure 3

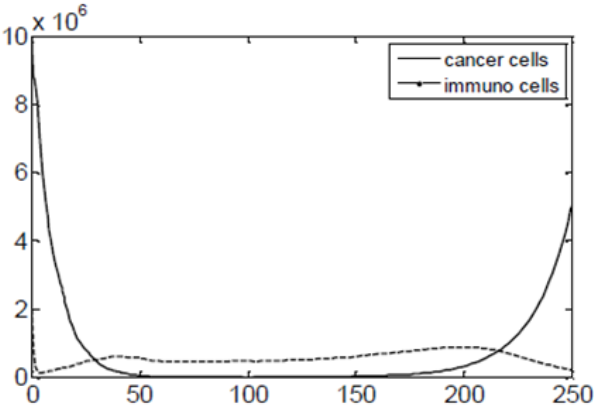

Fig.5.Model drag dosage Lyapunov criteria in accordance with the new conditions and change in concentration and toxicity drug dosage

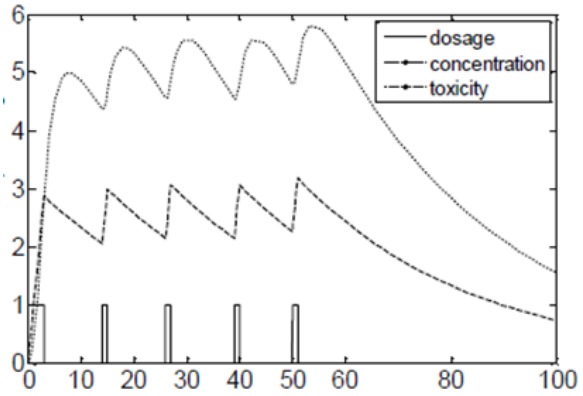

Fig.6. Change in the total population of cancer cells and immune cells in the model drag dosage Figure5

It can be seen that to keep the system in good condition of the drug, it should continue to be on going. But to do so due to an increase in side effects and toxicity in the body is virtually impossible, therefore since the physicians of chemotherapy until the cancer cells continue to be higher, the amount specified, in order to improve the condition of other drug obtained from case of exponent was added so that after reaching zero the number of cancer cells stops (fig. 5). The main problem in this case is that after the use of the drug control law, the possibility of the growth of cancer cells and to reaches a significant number there (fig. 6). To solve this problem, two solutions are recommended: First, it can be passed after a certain number of cancer cells than chemotherapy again resumed. This continued weakness of the patients and increased the toxicity of the drug in the body. The second solution is using

therapeutic vaccine after the period of chemotherapy. Vaccine therapy can change the parameters of the health system and strengthening the balance point.

6- Conclusion

In this study, a new mathematical model to describe the growth of cancer cells and immune cells as well as proposed changes in the concentration and toxicity of the drug and applying Lyapunor stability theorm, the optimal treatment protocol, was designed. To prevent re-growth of the system, parameters and the optimal balance point should be sustainable. Immune cells as well as proposed changes in the concentration and toxicity of the drug and applying Lyapunor stability theorm, the optimal treatment protocol was designed. To prevent re-growth of the system parameters and the optimal balance point should be sustainable.

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